

Atty. Dkt. No. 074066-0115

**Remarks**

The present invention relates to preservation solutions and methods for preserving cells, tissues, and organs. The solutions contain a combination of polyglycerol and lactose. The present inventor discovered unexpectedly that combining polyglycerol with lactose at concentrations effective to preserve cells, tissues, and organs under hypothermic conditions results in unexpected beneficial effects over prior art compositions and methods. Example 2 and Figure 3 of the present specification illustrate these unexpected effects. When rabbit kidneys were preserved with the solution of the present invention, the kidneys preserved with polyglycerol and lactose performed unequivocally better than those preserved with other preservation solutions. Kidneys preserved with the solution of the present invention produced no postoperative serum creatinine values higher than 3.5 mg/dl, whereas over half of the transplants using prior art preservation solutions resulted in creatinines exceeding 4.0 mg/dl (specification, p. 12, lines 18-31). Furthermore, kidneys preserved with a solution of the present invention exhibited superior reabsorptive capacity versus those preserved with prior art preservation solutions (specification, page 13, lines 3-9).

Claims 67 and 68 are added, and claim 58 is cancelled without prejudice to further prosecution. After this amendment, claims 1-6, and 36-57, and 59-68 are pending in the application.

The Examiner rejects claims 2 and 51 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite due to the recitation of "alpha lactose" (claim 2) and "impermeant species" (claim 51). The amendment of Claim 2 renders this rejection moot. While the

Atty. Dkt. No. 074066-0115

Applicant does not agree with the Examiner's assertion, claim 2 is amended solely in order to remove issues from the case and secure quick allowance of clearly allowable subject matter.

With respect to claim 51, Applicant respectfully disagrees with the Examiner's assertion that the meaning of "impermeant" is uncertain. It is understood by those of ordinary skill in the art that molecules can be classified based on their behavior in a particular context. If permeation is very slow compared to the amount of a compound present, it is normal to consider the compound to be impermeant in practice, even though it is not completely unable to permeate cells. A small amount of glucose present in a solution may permeate completely in a reasonable amount of time, but a large amount of glucose may remain primarily impermeant with only a small fraction crossing the membrane through facilitated membrane transport molecules whose maximum carrying capacity is orders of magnitude lower than would be required to transport the bulk of the added glucose. These points are understood by persons of ordinary skill in the art. In the context of the specification, the person of ordinary skill realizes that molecules such as glucose, lactose, polyglycerol, and citrate are impermeant, since they do not effectively permeate cells when used in the preservation solution. Indeed, the Khirabadi reference cited by the Examiner in the present case provides an example that these definitions are well understood in the art. Khirabadi provides a definition of "non-penetrating" precisely in this widely understood manner, stating "non-penetrating means that the great majority of molecules of the chemical do not penetrate into the cells of the blood vessel but instead remain in the extracellular fluid of the tissue." (Col. 9, lines 16-19). Furthermore, reference is made at several points in the specification to glucose and citrate as "impermeants" even while acknowledging that these agents permeate slowly (p. 8, line 26; p. 14, line 5; p. 18, line 19). Applicant therefore submits that the person of ordinary skill readily understands the terms used in the claims and the bounds of the claim as written.

Atty. Dkt. No. 074066-0115

The Examiner rejects claims 1-6 and 36-51 under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 6, 18, and 21 in co-pending application Serial No. 09/916,396. The Applicants will submit a terminal disclaimer in the present case with respect to co-pending case 09/916,396, if the claims in the co-pending case issue first and in their present form, and the present claims are otherwise allowable in their present form.

The Examiner rejects claims 1-4 and 6 under 35 U.S.C. 103(a) as allegedly being unpatentable over either Klebe (*In vitro*, Vol. 19 No. 3 (Part I), March 1983, pp. 167-171) or U.S. Patent No. 6,616,858 (Fahy) in view of U.S. Patent No. 6,194,137 (Khirabadi). This rejection is respectfully traversed. While the rejection is worded in a manner that suggests that the '858 patent or Klebe are the primary reference(s) and Khirabadi is the secondary reference, the form of the discussion that follows suggests that Khirabadi is intended to be the primary reference. Accordingly, the following argument assumes that the Examiner intended Khirabadi to be the primary reference. If such an interpretation is incorrect, clarification is respectfully requested.

The present invention, as defined by the present claims, distinguishes over the art by requiring methods (e.g., claims 52, 53, and 64, and those depending on these) and preservation solutions (e.g., claim 1 and claims dependent on claim 1) for cells, tissues, and organs that contain a combination of polyglycerol and lactose. The present inventor discovered unexpectedly that combining polyglycerol with lactose at concentrations effective to preserve cells, tissues, and organs under hypothermic conditions results in unexpected beneficial effects

Atty. Dkt. No. 074066-0115

over prior art, such as superior preservation of organs that retain greater organ activity after preservation.

Khirabadi does not disclose the combination of polyglycerol with lactose for any purpose. Khirabadi discloses only a "laundry list" of 11 impermeable chemicals having cryoprotective activity (Col. 6, lines 39-42). Lactose is but one of the 11 compounds provided in the "laundry list." No motivation is provided for selecting lactose among the 11 options on the list nor for combination of any of the 11 options on the list with polyglycerol. Instead, in his preferred embodiment Khirabadi points the user to VS55 for cryopreservation, which contains neither polyglycerol nor lactose, Col. 6, lines 43-49.

Klebe does not disclose the combination of lactose and polyglycerol. Klebe merely discloses a list of 31 compounds that were identified as cryoprotective agents for cultured CHO cells. Decaglycerol is but one of the 31 compounds listed by Klebe as having cryoprotective properties with regard to CHO cells cooled to -80C. Klebe does not describe decaglycerol as having any particularly beneficial effects or properties over the other 30 compounds on the list. In fact, Klebe showed that decaglycerol had only about half the cryoprotective activity of glucose,  $\frac{1}{4}$  that of sucrose,  $\frac{1}{5}^{\text{th}}$  -  $\frac{1}{6}^{\text{th}}$  that of dextran or polyethylene glycol of the same molecular weight as decaglycerol,  $\frac{1}{10}^{\text{th}}$  that of PEG methyl ester, about  $\frac{1}{20}^{\text{th}}$  that of PVP,  $\frac{1}{22}^{\text{nd}}$  that of PEG-3000, and  $\frac{1}{38}^{\text{th}}$  that of ethylene glycol in Klebe's assay system. Therefore, the person of ordinary skill finds no motivation to combine decaglycerol from Klebe with lactose from Khirabadi.

Finally, while Fahy is acknowledged as a significant advance in the art, only the present invention recognizes the benefits of combining polyglycerol with lactose in preservation solutions and methods of preserving cells, tissues and organs.

Atty. Dkt. No. 074066-0115

The references cited by the Examiner do not provide any advantage to be obtained by modifying Khirabadi as the Examiner suggests. Thus, no motivation has been provided for combining the polyglycerol from Fahy or Klebe with the lactose from Khirabadi. Such a combination would require the selection of lactose from Khirabadi out of a list of several compounds, even where Khirabadi directs the reader to other compositions containing ingredients not included on the list (Col. 6, line 43). Furthermore, no motivation is provided to select lactose for combination with a polyglycerol. Furthermore, making this combination would also require the additional extraordinary selection of decaglycerol from the list of 31 compounds provided by Klebe for combination with lactose, again without any motivation to do so. None of the references suggest any advantage to be gained by making this combination.

MPEP 2143 states that, to establish a prima facie case of obviousness, there must be a motivation, in the references or in the knowledge of the person of ordinary skill in the art, to make the modification or combination. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Yet the references allude to no advantage to be obtained by modifying Khirabadi as the Examiner suggests. The Applicant also points out that the fact that references can be combined or modified does not render the combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Indeed, the Federal Circuit has rendered a number of decisions overturning obviousness rejections due to a lack of suggestion in the prior art of the desirability of combining references. MPEP 2145(X)(C).

Thus, the combination asserted by the Examiner can be made only based on a hindsight reconstruction of the invention, which is not permitted by the patent laws. *In re McLaughlin*, 443

Atty. Dkt. No. 074066-0115

F.2d 1392, 1395; 179 USPQ 209,221 (CCPA 1971). Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.